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| BANNER & WITCOFF 1001 G STREET N W SUITE 1100 WASHINGTON, DC 20001 | | | HUYNH, PHUONG N | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|---------------------------------|------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/804,464 | KUNDIG ET AL. |
| | Examiner "Neon" Phuong Huynh | Art Unit 1644 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 30 April 2002.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-15, 19-26, 45 and 46 is/are pending in the application.
- 4a) Of the above claim(s) 11-13 and 15 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-10, 14, 19-26, 45 and 46 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____ .
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 . 6) Other: _____ .

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DETAILED ACTION

1. Claims 1-15, 19-26 and 45-46 are pending.
2. Applicant's election without traverse of Group I, claims 1-10, 14 and 16-42 (now claims 1-10, 14, 19-26 and 45-46) drawn to a method of modulating an allergic response of an individual comprising delivering an allergen directly into a lymph node of said individual wherein the allergen is bee venom that read on alum as the specific adjuvant, filed 4/30/02, is acknowledged.
3. Claims 11-13 and 15 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.
4. Claims 1-10, 14, 19-26, 45 and 46 drawn to a method of modulating an allergic response of an individual comprising delivering an allergen directly into a lymph node of said individual wherein the allergen is bee venom that read on alum as the specific adjuvant are being acted upon in this Office Action.
5. The drawings, filed 3/13/01, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.
6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration by inventor Stephen McCormack. See 37 CFR 1.52(c).
7. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The recitation of "0.01 µg" in original claim 23 has no support in the specification as filed. It is suggested that Applicants amend the specification to provide proper antecedent basis for the claimed subject matter.

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8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-10, 14, 19-26 and 45-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of modulating an allergic response of an individual comprising the step of injecting a specific allergen such as phospholipase A2 purified from bee venom directly into a lymph node such as the axillary lymph node, or the inguinal lymph node wherein said phospholipase A2 is delivered to the antigen presenting cell or immune cell within the lymph node of said individual whereby said modulating is an increase in antigen specific IgG2a and a decrease in antigen specific IgE, **does not** reasonably provide enablement for (1) a method of “modulating” *any* allergic response of an individual comprising the step of delivering *any* allergen, *any* extract or *any* purified substance, *any* recombinant protein and *any* synthesized peptide directly into a lymph node of said individual, whereby *any* allergic response is “modulated”, (2) the said method wherein said lymph node is an axillary lymph node, an inguinal lymph node, (3) the said method where said allergen is delivered to an antigen presenting cell within the lymph node using ultrasound device to monitor location of an injection needle, (4) the said method further comprising the step of visualizing the lymph node using a radiological method, (5) the said method wherein the allergen further comprises *any* delivery substance, (5) the said method wherein the allergen is accompanied by an adjuvant, (6) the said method wherein the step of delivering is carried out at least twice, (7) the said method wherein 1 to 5 doses of from about 0.1 µg to about 10 µg, from about 0.1 µg to about 50 µg of the allergen is administered, (8) the said method wherein the allergen is delivered in fewer than about 10 doses, or from 1 to about 5 doses and (9) the said method wherein the allergen is delivered into the lymph node with a syringe or a dual-chambered syringe for “modulating” *any* allergic response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable

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one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of modulating an allergic response of an individual comprising injecting phospholipase A2, which is an allergic component of bee venom, to the axillary or inguinal lymph node by delivering said allergen to an antigen presenting cell or an immune cell within the lymph node, using a syringe and an ultrasound device to monitor the location of an injection needle, and/or visualizing the lymph node using a radiological method wherein the modulating is an increase in bee venom phospholipase A2 specific IgG2a and a decrease in IgE activity. The specification discloses bee sting challenge only produces a minimum local reaction in a patient who has been desensitized.

The specification does not teach how to make and use *any* allergen, *any* extract or *any* purified substance, *any* recombinant protein and *any* synthesized peptide for a method of "modulating" *any* immune response. The term "modulating" could be increase or decrease and they are mutually exclusive. Further, there is insufficient guidance and working example as to the structure of *any* allergen, *any* extract or *any* purified substance, *any* recombinant protein and *any* synthesized peptide, let alone using it for increasing or decreasing *any* allergic immune responses.

Guidry *et al* teach lymph node injection of a substance such as *Staphylococcus aureus* significantly increase IgG2 response and the IgG2 response was slower and peak later than that for IgG1 (See page 2968, column 1, results, in particular). Guidry *et al* teach lymph node injection fails to elicit IgA response although IgA tended to be slightly higher than the IgM response. Given the indefinite number of undisclosed allergen, extract, substance, recombinant protein and synthesized peptide, it is unpredictable which undisclosed substance, recombinant protein, synthesized peptide mentioned above would be useful for modulating an allergic response wherein the modulating could be increasing or decreasing any undisclosed immune response. Other than the specific allergen mentioned above, the method of modulating a specific allergic response using *any* allergen, *any* extract or *any* purified substance, *any* recombinant protein and *any* synthesized peptide is not enabled; it follows that the dose of *any* undisclosed allergen mentioned above is not enabled. It also follows that the method of modulating an allergic response further comprising the step of using an ultrasound device, or radiological method is not enable.

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For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

10. Claims 1-10, 14, 19-26 and 45-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of "modulating" *any* allergic response of an individual comprising the step of delivering *any* allergen, *any* extract or *any* purified substance, *any* recombinant protein and *any* synthesized peptide directly into a lymph node of said individual, whereby *any* allergic response is "modulated", (2) the said method wherein said lymph node is an axillary lymph node, an inguinal lymph node, (3) the said method where said allergen is delivered to an antigen presenting cell within the lymph node using ultrasound device to monitor location of an injection needle, (4) the said method further comprising the step of visualizing the lymph node using a radiological method, (5) the said method wherein the allergen further comprises *any* delivery substance, (5) the said method wherein the allergen is accompanied by an adjuvant, (6) the said method wherein the step of delivering is carried out at least twice, (7) the said method wherein 1 to 5 doses of from about 0.1 µg to about 10 µg, from about 0.1 µg to about 50 µg of the allergen is administered, (8) the said method wherein the allergen is delivered in fewer than about 10 doses, or from 1 to about 5 doses and (9) the said method wherein the allergen is delivered into the lymph node with a syringe or a dual-chambered syringe for modulating an allergic response.

The specification discloses only a method of modulating an allergic response of an individual comprising injecting phospholipase A2, which is an allergic component of bee venom, to the axillary or inguinal lymph node by delivering said allergen to an antigen presenting cell or

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an immune cell within the lymph node, using a syringe and an ultrasound device to monitor the location of an injection needle, or visualizing the lymph node using a radiological method wherein the modulating is an increase in bee venom phospholipase A2 specific IgG2a and a decrease in IgE activity. The specification discloses bee sting challenge only produces a minimum local reaction in a patient who has been desensitized.

With the exception of the specific allergen mentioned above, there is insufficient written description about the structure associated with function of *any* allergen, *any* extract or *any* purified substance, *any* recombinant protein and *any* synthesized peptide. Given that there is a lack of an additional species of allergen for a method of increasing phospholipase A2 specific IgG2a, and a decrease in IgE activity, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.
12. Claims 19 and 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "administered" recited in claims 23 and 24, line 2 has no antecedent basis in base claim 1. Only "delivering" is recited in base claim 1.

The recitation of "a delivery substance" in claim 19 is ambiguous and indefinite. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
15. Claims 1-5, 8-9, 14, 19-26 and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong *et al* (J Immunological Methods 120: 151-7, June 1989; PTO 892) in view of Hellman *et al* (Handbook of Experimental Pharmacology 133(vaccines): 499-526, 1999; PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892).

Hong *et al* teach a method of modulating an immune response of an individual such as increasing the production of antigen specific IgG class monoclonal antibodies by delivering an antigen such as human serum albumin (Has) directly into a an inguinal lymph node by injection using a syringe (See entire document, Materials and methods, in particular). The reference inguinal lymph node immunization increases the magnitude of primary immune response against the specific antigen (See page 153, column 2, first paragraph, in particular). The reference antigen further comprises a delivery substance such as Freund's complete or incomplete adjuvant or aluminum (See page 153, column 1, last paragraph, page 155 Table II, in particular). The reference method wherein the reference HAS was injected at 0.1 µg, 0.5 µg, 1 µg, 5 µg, 10 µg or 50 µg per doses (See page 153, column 1, last paragraph, in particular). The reference method delivering is carried out at least twice (See booster shot, secondary immunization, abstract, in particular). Hong *et al* teach the inguinal lymph node immunizations induces strong primary immune response with limited amounts of antigen (See abstract, page 152, column 1, first paragraph, in particular).

The claimed invention as recited in claim 1 differs from the reference only that the method of modulating an allergic response of an individual comprising the step of delivering an allergen directly into a lymph node of said individual whereby the allergic response is modulated.

The claimed invention as recited in claim 2 differs from the reference only that the lymph node is axillary lymph node.

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The claimed invention as recited in claim 4 differs from the reference only that the allergen is delivered to an antigen presenting cell within the lymph node.

The claimed invention as recited in claim 5 differs from the reference only that the allergen is delivered to an immune cell within the lymph node.

The claimed invention as recited in claim 8 differs from the reference only that the individual possesses defective lymph nodes.

The claimed invention as recited in claim 9 differs from the reference only that the allergen is an extract or a purified substance.

The claimed invention as recited in claim 14 differs from the reference only that the allergen is selected from the group consisting of a recombinant protein and a synthesized peptide.

The claimed invention as recited in claim 46 differs from the reference only that the individual possesses defective lymph nodes.

Hellman *et al* teach injection of the allergen such as pollen extract or recombinant protein or synthesized peptide can be effective for seasonal pollenosis by increasing allergen specific IgG, which is often correlated with reduced symptoms scores in the patient (See page 507, second paragraph, page 509, page 510, in particular). The increase in allergen specific IgG is the results of a shift in cytokine profile, with decreasing IL4 and IL-5 and increasing or unaffected levels of IFN- γ and IL-10 (See page 507, second paragraph, in particular). Hellman *et al* teach allergen specific IgG to redirect the immune response can significantly improve the clinical outcome for patient with chronic allergy and this beneficial effect can be maintained for a long time after the discontinuation of the therapy (See page 509, first paragraph, in particular).

Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* teach the reference method is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular).

Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

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Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the antigen as taught by Hong *et al* for the allergen as taught by Hellman *et al* for a method of modulating an allergic response by delivering any allergen directly into the antigen presenting cell or immune cells within the lymph node as taught by Hong *et al*, Coupey *et al* and Zinkernagel *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Hong *et al* teach the inguinal lymph node immunizations induces strong primary immune response with limited amounts of antigen (See abstract, page 152, column 1, first paragraph, in particular). Hellman *et al* teach injection of the allergen such as pollen extract can be effective for seasonal pollenosis by increasing allergen specific IgG, which is often correlated with reduced symptoms scores in the patient (See page 507, second paragraph, in particular). Coupey *et al* teach intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular) and the reference method is useful for obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) in order to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular). Claim 8 is included in this rejection because it is obvious that APC fails to migrate to the via the afferent lymph node in individual with defective lymph node since Zinkernagel *et al* teach antigens outside of the lymphoid tissues (lymph node) are immunologically ignored (See page 202, column 2, in particular). Claim 21 is included in this rejection because the reference adjuvant alumn is marketed in the form of aluminum hydroxide or phosphate. Claim 46 is included in this rejection because it is within the purview of one skilled in the art at the time the invention was made to use any syringe for injection as taught by Hellman *et al* and Coupey *et al*.

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16. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hong *et al* (J Immunological Methods 120: 151-7, June 1989; PTO 892) in view of Hellman *et al* (Handbook of Experimental Pharmacology 133(vaccines): 499-526, 1999; PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892) as applied to claims 1-5, 8-9, 14, 19-20, 22-26 and 45-46 mentioned above, and further in view of Banks *et al* (Chemistry and Pharmacology of Honey-bee venom In: Piek T, ed. Venoms of the Hymenoptera. London: Academic Press; 1986, pages 329-416).

The teachings of Hong *et al*, Hellman *et al*, Coupey *et al*, and Zinkernagel *et al* have been discussed supra.

The claimed invention as recited in claim 10 differs from the references only that the allergen is the allergenic components of bee venom.

Banks *et al* teach a method of modulating an immune response (desensitization) comprising administering a small but increasing amounts of allergenic components such as phospholipase A2 (the chief allergen in bee venom), hyaluronidase, melittin and protease inhibitor (See Table II, in particular) of bee venom to build up the IgG levels in the serum of a subject to inhibit an immune reaction (allergic reaction) against bee sting (See page 342, pages 331 and 403, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute antigen as taught by Hong *et al* or the pollen allergen as taught by Hellman *et al* for the allergenic components of bee venom for a method of modulating an allergic response to bee by delivering the allergen directly into a lymph node of any individual as taught by Hong *et al*, Coupey *et al* and Zinkernagel *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Banks *et al* teach administering a small but increasing amounts of allergenic components such as phospholipase A2 (the chief allergen in bee venom), hyaluronidase, melittin and protease inhibitor (See Table II, in particular) of bee venom can build up the IgG levels in the serum of a subject to inhibit an allergic response against bee sting (See page 342, pages 331 and 403, in particular).

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17. Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong *et al* (J Immunological Methods 120: 151-7, June 1989; PTO 892) in view of Hellman *et al* (Handbook of Experimental Pharmacology 133(vaccines): 499-526, 1999; PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892) as applied to claims 1-5, 8-9, 14, 19-20, 22-26 and 45-46 mentioned above, and further in view of WO 99/02183 (Jan 1999; PTO 1449).

The teachings of Hong *et al*, Hellman *et al*, Coupey *et al*, and Zinkernagel *et al* have been discussed supra.

The claimed invention as recited in claim 6 differs from the references only that the method step further comprising the use of an ultrasound device to monitor location of an injectable needle.

The claimed invention as recited in claim 7 differs from the references only that the method further comprising the step of visualizing the lymph node using a radiological method.

The WO 99/02183 publication teaches a method of delivering any antigen to the inguinal lymph node by inserting a catheter or needle under ultrasonographic control to monitor the location of the needle (See page 58, lines 14-27, in particular). The WO 99/02183 publication further teaches radiography may be used to image a patient's lymphatic flow to determine where the relatively high lymphatic drainage occurs in order to decide upon an insertion position that maximizes delivery into the lymphatic system (See page 60, lines 28-33, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the use of ultrasound device or radiographic method as taught by the WO 99/02183 publication for a method of modulating an allergic response of an individual comprising the step of delivering the allergen directly into a lymph node as taught by Hong *et al*, Hellman *et al*, Coupey *et al*, and Zinkernagel *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 99/02183 publication teaches the use of radiography can image a patient's lymphatic flow in order to decide upon an insertion position for maximizes delivery into the lymphatic system (See page 60, lines 28-33, in particular) and the ultrasonographic device can monitor the location of the needle (See page 58, lines 14-27, in particular).

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18. No claim is allowed.
19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.
20. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
July 15, 2002

Christina Chan
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